NOVARTIS

Initial REMS Approval: 9/2010
Most Recent Modification: 5/2013

NDA 22-527

GILENYA® (fingolimod) 0.5mg capsules

Sphingosine 1-phosphate Receptor Modulator

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

1 Goals

The goal of the GILENYA® (fingolimod) REMS is:

- To inform healthcare professionals (HCPs) about the serious risks of GILENYA (fingolimod) including bradyarrhythmia and atrioventricular (AV) block at treatment initiation, infections, macular edema, respiratory effects, hepatic effects, and fetal risk.

2 REMS Elements

2.1 Communication Plan

Novartis will implement a communication plan to HCPs to support implementation of the REMS. The communication plan includes the:

1. Dear Healthcare Professional Letter (DHCPL)

   This letter for prescribers includes information about the approved indication for GILENYA and describes the contraindications for use, the potential serious risks of the product, including bradyarrhythmia and AV block following initiation of treatment, infections, macular edema, respiratory effects, hepatic effects, and fetal risk. It also summarizes the specific recommendations and monitoring related to these risks, based on relevant sections of the revised Package Insert (PI) dated May 2012. The letter also includes information about the GILENYA Pregnancy Registry and encourages prescribers to register patients.

   The communication plan will target the following HCPs:

   > Potential prescribers of GILENYA: The main prescribers of GILENYA are neurologists with experience in treating patients with MS. A list of potential prescribers will be compiled from IMS data providing prescribers of MS drugs and the membership list from the Consortium of Multiple Sclerosis Centers.

2. Dear Professional Society Letter

   A letter will be provided to the leadership of the following professional societies: Consortium of Multiple Sclerosis Centers, the American Academy of Neurology, the American Neurology Association, and the National Multiple Sclerosis Society. The content of the letter will be the same as described above for the DHCPL, with the exception of the introduction and a statement describing that the leadership of the society should distribute the letter to their members.

3. Guide to Important Safety Information: Using GILENYA in Patients with Relapsing Forms of Multiple Sclerosis

This guide will present more detail on the safety information related to bradyarrhythmia and AV block following initiation of treatment, infections, macular edema, respiratory effects, hepatic effects, and fetal risk. It also highlights contraindications for GILENYA, information about each risk and guidance for prescribers related to monitoring and counseling of patients at treatment initiation and during GILENYA therapy. The guide also includes information about the GILENYA Pregnancy Registry and encourages prescribers to register patients.

4. GILENYA REMS website

The GILENYA REMS website (www.gilenyarems.com) will contain the current full Prescribing Information (PI), the DHCPL, the Dear Professional Society Letter, the Guide to Important Safety Information: Using GILENYA in Patients with Relapsing Forms of Multiple Sclerosis, and information about the GILENYA Pregnancy Registry.

Distribution of the DHCPL, Dear Professional Society Letter and the Guide to Important Safety Information will be sent by direct mail via the US Postal Service regular mail according to the following timeline:

a) Within 30 days of this REMS modification approval by FDA

b) And then, annually from the date of the initial REMS approval (September 21, 2010) for a period of 5 years.

c) Novartis will ensure that all materials listed in or appended to the GILENYA REMS will be available through the GILENYA REMS website. This information will be available on the website for 5 years from the date of initial approval. All of these materials will also be available by request through Novartis's toll-free information number (1-888-NOW-NOVA or 1-888-669-6682), through Novartis sales representatives and field-based medical personnel.

The following materials are part of the REMS and are appended:

(i) DHCPL
(ii) Dear Professional Society Letter
(iii) Guide to Important Safety Information: Using GILENYA in Patients with Relapsing Forms of Multiple Sclerosis
(iv) GILENYA REMS website

3 Timetable for Submission of Assessments

REMS assessments will be submitted to FDA at 18 months, 3 years, 4 years, and 7 years from the initial date of approval of the REMS (September 21, 2010). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the

reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for each assessment time interval. Novartis will submit each assessment so that it will be received by the FDA on or before the due date.

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(fingolimod) les

Please read the following materials:

- PRESCRIBING INFORMATION
- DEAR HEALTHCARE PROFESSIONAL LETTER
- DEAR PROFESSIONAL SOCIETY LETTER
- GUIDE TO IMPORTANT SAFETY INFORMATION
- GILENYA PREGNANCY REGISTRY

Risk Evaluation and Mitigation Strategy (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

In order for Novartis Pharmaceuticals Corporation to communicate certain risks about GILENYA, we have worked with the FDA to develop materials to communicate the risks of:

- Bradyarrhythmia and Atrioventricular (AV) Block
- Infections
- Macular Edema
- Respiratory Effects
- Hepatic Effects
- Fetal Risk

Attachment C: Dear Professional Society Letter

XX (Month) 2013

IMPORTANT DRUG WARNING

Please disseminate this information to your members

Subject: Risk of bradyarrhythmia and atrioventricular block at treatment initiation: recommendations for first dose monitoring; contraindications; recommendations for patients with coexisting medical condition or certain concomitant medications

Reminder: infections, macular edema, respiratory effects, hepatic effects, and fetal risk with GILENYA® (fingolimod)

FDA-Required Risk Evaluation and Mitigation Strategy (REMS)

Dear Professional Society:

The purpose of this letter is to remind you of important safety information for GILENYA, based on the May 2012 prescribing information.

GILENYA is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. GILENYA is a sphingosine 1-phosphate receptor (S1P) modulator. GILENYA blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood to approximately 30% of baseline values. The mechanism by which fingolimod exerts therapeutic effects in MS is unknown, but may involve reduction of lymphocyte migration into the central nervous system.

Bradyarrhythmia and Atrioventricular (AV) Block

Initiation of Gilenya treatment results in a decrease in heart rate. In controlled studies, Gilenya has also been associated with AV conduction delays, including first or second degree AV block, following initiation of treatment. After the first dose of GILENYA, the heart rate decrease starts within an hour and the Day 1 nadir generally occurs within approximately 6 hours, although the nadir can be observed up to 24 hours after the first dose in some patients. Adverse reactions of symptomatic bradycardia following the first dose were reported in 0.5% of patients receiving GILENYA 0.5 mg, but in no patient on placebo.

Recommendations for first dose monitoring

When beginning treatment with GILENYA:

- All patients should be observed for signs and symptoms of bradycardia for a period of at least 6 hours after the first dose of GILENYA.
- Hourly blood pressure and pulse measurements should be obtained during this timeframe.
- All patients should have an electrocardiogram (ECG) prior to the first dose of GILENYA and after the 6 hour observation period.
- Patients with a heart rate < 45 bpm or new onset 2nd degree or higher AV block at 6 hours post-dose or patients registering the lowest post-dose heart rate at the end of the observation period should be monitored until resolution of the finding.
- In patients experiencing post dose symptomatic bradycardia, continuous ECG monitoring should be instituted along with initiation of appropriate treatment and observation until the symptoms have resolved; if pharmacological intervention is required to treat symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and first-dose monitoring procedures should be repeated after the second dose of GILENYA.
- Patients at higher risk of symptomatic bradycardia or bradyarrythmia due to coexisting medical conditions or certain concomitant medications should have a cardiac evaluation and, if treated with GILENYA, should be observed overnight in a medical facility with continuous ECG monitoring.
- Patients with prolonged QTc interval at baseline or during the observation period, or at additional risk for QT prolongation or taking drugs with known risk of torsades de pointes should be observed overnight in a medical facility with continuous ECG monitoring.
- Patients receiving concomitant therapies that slow heart rate or AV conduction should be evaluated with possibility of switching off these drugs prior to initiation of GILENYA. In patients who cannot switch overnight observation in a medical facility with continuous ECG monitoring is recommended.

Re-initiation of therapy following discontinuation

If GILENYA therapy is discontinued for more than 14 days after the first month of treatment, the effects on heart rate and AV conduction may recur on reintroduction of GILENYA treatment and the same precautions (first-dose monitoring) as for initial dosing should apply. Within the first 2 weeks of treatment, first-dose procedures are recommended after interruption of one day or more; during week 3 and 4 of treatment first- dose procedures are recommended after treatment interruption of more than 7 days.

Contraindications

GILENYA is contraindicated in patients

- with recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure
- with a history or presence of Mobitz Type II 2nd or 3rd degree AV block or sick sinus syndrome, unless the patient has a functional pacemaker
- with a baseline QTc interval ≥ 500 msec
- receiving treatment with Class Ia or Class III anti-arrhythmic drugs

We also remind you of the other important safety information for GILENYA

Infections

GILENYA causes a dose-dependent, reversible sequestration of lymphocytes in lymphoid tissues resulting in a reduction of peripheral blood lymphocyte count to 20 - 30% of baseline values.

- Before initiating treatment with GILENYA, a recent CBC (i.e. within the last 6 months) should be available.
- Consider suspending treatment with GILENYA if a patient develops a serious infection, and reassess the benefits and risks prior to re-initiation of therapy.
- Patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody negative patients should be considered prior to commencing treatment with GILENYA, following which initiation of treatment with GILENYA should be postponed for one month to allow for full effect of vaccination to occur.
- The use of live attenuated vaccines should be avoided during and for 2 months after treatment with GILENYA because of the risk of infection.

Macular Edema

In clinical trials, macular edema occurred in 0.4% of patients who received GILENYA 0.5mg, predominantly within the first 3-4 months. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmologic examination. Macular edema generally improved or resolved with or without treatment after drug discontinuation, but some patients had residual visual acuity loss even after resolution of macular edema.

- An adequate ophthalmologic evaluation should be performed at baseline and 3-4 months after treatment initiation.
- If patients report visual disturbances at any time while taking GILENYA, additional ophthalmologic evaluation should be undertaken.
- Patients who have a history of uveitis or diabetes are at increased risk of macular edema. MS patients with diabetes mellitus or a history of uveitis should undergo an ophthalmologic evaluation prior to initiating therapy and have regular follow-up ophthalmologic evaluations while receiving GILENYA therapy.

Respiratory Effects

Small dose-dependent reductions in forced expiratory volume over one second (FEV1) and Diffusion Capacity of the Lung for Carbon Monoxide (DLCO) were observed in patients treated with GILENYA, as early as 1 month after treatment initiation. The changes in FEV1 appear to be reversible after treatment discontinuation. There is insufficient information to determine the reversibility of the decrease of DLCO after drug discontinuation.

- Spirometric evaluation of respiratory function and evaluation of diffusion lung capacity for carbon monoxide (DLCO) should be performed during therapy with GILENYA if clinically indicated.

Hepatic Effects

Elevations of liver function tests may occur in patients receiving GILENYA. The majority of elevations occurred within 6-9 months.

- Recent (i.e. within the last 6 months) transaminase and bilirubin levels should be available before initiation of GILENYA therapy.
- Liver enzymes should be monitored in patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. GILENYA should be discontinued if significant liver injury is confirmed. Patients with pre-existing liver disease may be at increased risk of developing elevated liver function tests when taking GILENYA.

Fetal Risk

Based on animal studies, GILENYA may cause fetal harm.

- There are no adequate and well-controlled studies of GILENYA in pregnant women.
- Women of childbearing potential should be counseled on the potential risk to the fetus and advised to use effective contraception during and for at least 2 months following discontinuation of GILENYA therapy.
- Women who become pregnant while on therapy must be counseled on potential risk to the fetus.
- GILENYA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy registry

Since there are no adequate and well-controlled studies of GILENYA in pregnant women, a pregnancy registry has been established to collect information about the effects of GILENYA during pregnancy. Physicians are encouraged to register patients who become pregnant while exposed to GILENYA or within 2 months after stopping therapy. Prescribers with an eligible patient, or patients themselves, can contact the Pregnancy Exposure Registry by calling Outcome at 1-877-598-7237, sending an email to gpr@outcome.com or visiting www.gilenyapregnancyregistry.com.

Reporting adverse events

To report all suspected adverse events associated with the use of GILENYA contact:

- Novartis Drug Safety & Epidemiology at 1-888-NOW-NOVA (669-6682)
- FDA at 1-800-FDA-1088 or www.fda.gov/ medwatch.

Please see the accompanying complete updated Prescribing Information and Medication Guide. For more information regarding GILENYA, please contact Novartis Medical Information and Communication at 1-888-NOW-NOVA (669-6682) or visit the website at www.GILENYA.com.

Sincerely,

Ralph Kern, MD
VP and Head MS Medical Unit
Novartis Pharmaceuticals Corporation

Attachment B: Dear Healthcare Professional Letter (DHCPL)

XX (Month) 2013

IMPORTANT DRUG WARNING

Subject: Risk of bradyarrhythmia and atrioventricular block at treatment initiation: recommendations for first dose monitoring; contraindications; recommendations for patients with coexisting medical condition or certain concomitant medications

Reminder: infections, macular edema, respiratory effects, hepatic effects, and fetal risk with GILENYA® (fingolimod)

FDA-Required Risk Evaluation and Mitigation Strategy (REMS)

Dear Healthcare Professional:

The purpose of this letter is to remind you of important safety information for GILENYA, based on the May 2012 prescribing information.

GILENYA is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. GILENYA is a sphingosine 1-phosphate receptor (S1P) modulator. GILENYA blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood to approximately 30% of baseline values. The mechanism by which fingolimod exerts therapeutic effects in MS is unknown, but may involve reduction of lymphocyte migration into the central nervous system.

Bradyarrhythmia and Atrioventricular (AV) Block

Initiation of Gilenya treatment results in a decrease in heart rate. In controlled studies, Gilenya has also been associated with AV conduction delays, including first or second degree AV block, following initiation of treatment. After the first dose of GILENYA, the heart rate decrease starts within an hour and the Day 1 nadir generally occurs within approximately 6 hours, although the nadir can be observed up to 24 hours after the first dose in some patients. Adverse reactions of symptomatic bradycardia following the first dose were reported in 0.5% of patients receiving GILENYA 0.5 mg, but in no patient on placebo.

Recommendations for first dose monitoring

When beginning treatment with GILENYA:

- All patients should be observed for signs and symptoms of bradycardia for a period of at least 6 hours after the first dose of GILENYA.
- Hourly blood pressure and pulse measurements should be obtained during this timeframe.
- All patients should have an electrocardiogram (ECG) prior to the first dose of GILENYA

and after the 6 hour observation period.

- Patients with a heart rate < 45 bpm or new onset 2nd degree or higher AV block at 6 hours post-dose or patients registering the lowest post-dose heart rate at the end of the observation period should be monitored until resolution of the finding.
- In patients experiencing post dose symptomatic bradycardia, continuous ECG monitoring should be instituted along with initiation of appropriate treatment and observation until the symptoms have resolved; if pharmacological intervention is required to treat symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and first-dose monitoring procedures should be repeated after the second dose of GILENYA.
- Patients at higher risk of symptomatic bradycardia or bradyarrythmia due to coexisting medical conditions or certain concomitant medications should have a cardiac evaluation and, if treated with GILENYA, should be observed overnight in a medical facility with continuous ECG monitoring.
- Patients with prolonged QTc interval at baseline or during the observation period, or at additional risk for QT prolongation or taking drugs with known risk of torsades de pointes should be observed overnight in a medical facility with continuous ECG monitoring.
- Patients receiving concomitant therapies that slow heart rate or AV conduction should be evaluated with possibility of switching off these drugs prior to initiation of GILENYA. In patients who cannot switch overnight observation in a medical facility with continuous ECG monitoring is recommended.

Re-initiation of therapy following discontinuation

If GILENYA therapy is discontinued for more than 14 days after the first month of treatment, the effects on heart rate and AV conduction may recur on reintroduction of GILENYA treatment and the same precautions (first-dose monitoring) as for initial dosing should apply. Within the first 2 weeks of treatment, first-dose procedures are recommended after interruption of one day or more; during week 3 and 4 of treatment first- dose procedures are recommended after treatment interruption of more than 7 days.

Contraindications

GILENYA is contraindicated in patients

- with recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure
- with a history or presence of Mobitz Type II 2nd or 3rd degree AV block or sick sinus syndrome, unless the patient has a functional pacemaker
- with a baseline QTc interval ≥ 500 msec
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We also remind you of the other important safety information for GILENYA

Infections

GILENYA causes a dose-dependent, reversible sequestration of lymphocytes in lymphoid tissues resulting in a reduction of peripheral blood lymphocyte count to 20 - 30% of baseline values.

- Before initiating treatment with GILENYA, a recent CBC (i.e. within the last 6 months) should be available.
- Consider suspending treatment with GILENYA if a patient develops a serious infection, and reassess the benefits and risks prior to re-initiation of therapy.
- Patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody negative patients should be considered prior to commencing treatment with GILENYA, following which initiation of treatment with GILENYA should be postponed for one month to allow for full effect of vaccination to occur.
- The use of live attenuated vaccines should be avoided during and for 2 months after treatment with GILENYA because of the risk of infection.

Macular Edema

In clinical trials, macular edema occurred in 0.4% of patients who received GILENYA 0.5mg, predominantly within the first 3-4 months. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmologic examination. Macular edema generally improved or resolved with or without treatment after drug discontinuation, but some patients had residual visual acuity loss even after resolution of macular edema.

- An adequate ophthalmologic evaluation should be performed at baseline and 3-4 months after treatment initiation.
- If patients report visual disturbances at any time while taking GILENYA, additional ophthalmologic evaluation should be undertaken.
- Patients who have a history of uveitis or diabetes are at increased risk of macular edema. MS patients with diabetes mellitus or a history of uveitis should undergo an ophthalmologic evaluation prior to initiating therapy and have regular follow-up ophthalmologic evaluations while receiving GILENYA therapy.

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Hepatic Effects

Elevations of liver function tests may occur in patients receiving GILENYA. The majority of elevations occurred within 6-9 months.

- Recent (i.e. within the last 6 months) transaminase and bilirubin levels should be available before initiation of GILENYA therapy.
- Liver enzymes should be monitored in patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. GILENYA should be discontinued if significant liver injury is confirmed. Patients with pre-existing liver disease may be at increased risk of developing elevated liver function tests when taking GILENYA.

Fetal Risk

Based on animal studies, GILENYA may cause fetal harm.

- There are no adequate and well-controlled studies of GILENYA in pregnant women.
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- Women who become pregnant while on therapy must be counseled on potential risk to the fetus.
- GILENYA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy registry

Since there are no adequate and well-controlled studies of GILENYA in pregnant women, a pregnancy registry has been established to collect information about the effects of GILENYA during pregnancy. Physicians are encouraged to register patients who become pregnant while exposed to GILENYA or within 2 months after stopping therapy. Prescribers with an eligible patient, or patients themselves, can contact the Pregnancy Exposure Registry by calling Outcome at 1-877-598-7237, sending an email to gpr@outcome.com or visiting www.gilenyapregnancyregistry.com.

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To report all suspected adverse events associated with the use of GILENYA contact:

- Novartis Drug Safety & Epidemiology at 1-888-NOW-NOVA (669-6682)
- FDA at 1-800-FDA-1088 or www.fda.gov/ medwatch.

Please see the accompanying complete updated Prescribing Information and Medication Guide. For more information regarding GILENYA, please contact Novartis Medical Information and Communication at 1-888-NOW-NOVA (669-6682) or visit the website at www.GILENYA.com.

Sincerely,

Ralph Kern, MD
VP and Head MS Medical Unit
Novartis Pharmaceuticals Corporation

(Note to reviewer: This is a tri-fold brochure that has been submitted in Word format for review.)

(Month) 2013

Guide to Important Safety Information

Using GILENYA®
In Patients with Relapsing Forms of Multiple Sclerosis

Novartis Pharmaceuticals Corporation (Novartis), in collaboration with the Food and Drug Administration, developed a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of GILENYA outweigh the risks. This Guide to Important Safety Information is provided to you as part of the REMS and is revised based on the full prescribing information updated May 2012. The purpose of this guide is to highlight safety issues and provide a summary of recommendations healthcare professionals should consider before prescribing GILENYA. Please review the **full prescribing information (updated May 2012)** for detailed safety information for GILENYA.

SUMMARY OF RECOMMENDATIONS*

TIMING	RECOMMENDATION
Considerations prior to initiating treatment	☐ GILENYA treatment is **contraindicated** in patients: ▪ with recent (within last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure ▪ with a history or presence of Mobitz Type II 2nd or 3rd degree AV block or sick sinus syndrome, unless patient has a functioning pacemaker ▪ with a baseline QTc interval ≥500 msec ▪ receiving treatment with Class Ia or III anti-arrhythmic drugs ☐ The first dose of GILENYA should be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available ☐ All patients should have an electrocardiogram (ECG) prior to the first dose of GILENYA and at the end of the observation period ☐ Recent (i.e. within 6 months) CBC should be available ☐ Recent (i.e. within 6 months) liver transaminase and bilirubin levels should be available ☐ Baseline ophthalmologic examination ☐ Women of childbearing potential: Counsel on potential for adverse fetal outcomes and need for contraception ☐ Patients without a history of chicken pox or without vaccination against varicella zoster virus (VZV): Consider serology. If patient is antibody negative, VZV vaccine should be considered. ☐ Patients who get VZV vaccination should not begin GILENYA treatment

	for one month
Treatment initiation (first dose)	☐ Monitor blood pressure and pulse hourly ☐ Observe all patients for signs and symptoms of bradycardia for a period of at least 6 hours after the first dose of GILENYA ☐ All patients should have an ECG prior to and after the 6 hour observation period ☐ Continue observation beyond 6 hours (until resolution) if: ▪ the lowest post-dose heart rate is observed at end of the observation period ▪ heart rate is < 45 bpm ▪ new onset of 2nd degree or higher AV block (Refer to full **Prescribing Information updated May 2012** for management of patients experiencing symptomatic bradycardia) ☐ Overnight observation in a medical facility with continuous ECG monitoring should be initiated in: ▪ Patients at a higher risk for symptomatic bradycardia or bradyarrhythmia due to coexisting medical conditions (refer to full PI) ▪ Patients receiving concurrent therapies that slow heart rate or AV conduction should be evaluated with possibility of switching off these drugs prior to initiation of GILENYA. In patients who cannot switch, this observation is recommended. ▪ Patients with prolonged QTc interval at baseline or during the observation period, or taking drugs with known risk of torsades de pointes or at additional risk for QT prolongation
During treatment	☐ Monitor blood pressure ☐ Instruct patients to report symptoms of infection ☐ Avoid live attenuated vaccines ☐ Perform ophthalmologic examination 3-4 months after starting GILENYA, and at any time if patient reports visual disturbances. Perform regular follow-up ophthalmologic evaluations in patients with diabetes mellitus or a history of uveitis. ☐ Counsel women of childbearing potential about the importance of contraception use ☐ Obtain spirometric evaluation of respiratory function and diffusion lung capacity for carbon monoxide (DLCO) if clinically indicated ☐ Monitor liver enzymes in patients who develop symptoms suggestive of hepatic dysfunction ☐ Continue to be alert to patient reports of cardiac symptoms. Clinical data show effects of GILENYA on heart rate are maximal after first dose. Milder effects on heart rate may persist for, on average, 2-4 weeks after initiation of treatment when heart rate generally returns to baseline.

After treatment discontinuation	☐ Instruct patients to report symptoms of infection for up to 2 months ☐ If GILENYA therapy is discontinued for more than 14 days after the first month of treatment, the effects on heart rate and AV conduction may recur on reintroduction of GILENYA treatment and the same precautions (first dose monitoring) as for initial dosing should apply. Within the first 2 weeks of treatment, first dose procedures are recommended after interruption of one day or more. During week 3 and 4 of treatment, first dose procedures are recommended after treatment interruption of more than 7 days. ☐ Counsel women of childbearing potential on need for continuing contraception for 2 months

*Please see the accompanying complete updated full Prescribing Information (**updated May 2012**) for more information.

GILENYA® (fingolimod) is a sphingosine 1-phosphate receptor (S1P) modulator indicated for treatment of patients with relapsing forms of multiple sclerosis (MS). GILENYA has been shown to reduce the frequency of clinical exacerbations and delay the accumulation of physical disability in these patients.

Novartis is providing the following information concerning potential risks to consider when prescribing GILENYA:

IMPORTANT SAFETY INFORMATION

Bradyarrhythmia and Atrioventricular (AV) Block

GILENYA, in controlled studies, was shown to induce a reduction in heart rate and has been associated with AV conduction delays including 1st or 2nd degree AV block following administration of the initial dose. After the first dose of GILENYA, the heart rate decrease starts within an hour and the Day 1 nadir generally occurs within approximately 6 hours, although the nadir can be observed up to 24 hours after the first dose in some patients. Adverse reactions of symptomatic bradycardia following the first dose were reported in 0.5% of patients receiving GILENYA 0.5 mg, but no patient on placebo. The conduction abnormalities were usually transient and asymptomatic, and resolved within the first 24 hours on treatment. For these reasons, it has been recommended that all patients be observed for a period of at least 6 hours after the first GILENYA dose for signs and symptoms of bradyarrhythmia and AV block.

Recommendations for first dose monitoring

- All patients should be observed for signs and symptoms of bradycardia for a period of at least 6 hours after the first dose of GILENYA.
- Hourly blood pressure and pulse measurements should be obtained during this timeframe.
- All patients should have an electrocardiogram (ECG) prior to and at the end of the observation period.
- Patients with a heart rate < 45 bpm or new onset 2nd degree or higher AV block at 6 hours post-dose or patients registering the lowest post-dose heart rate at the end of the observation period
- should be monitored until resolution of the finding.
- In patients experiencing post dose symptomatic bradycardia, continuous ECG monitoring should be instituted along with initiation of appropriate treatment and observation until the symptoms have resolved; if pharmacological intervention is required to treat symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and first-dose monitoring procedures should be repeated after the second dose of GILENYA.
- Patients at higher risk of symptomatic bradycardia or bradyarrhythmia due to coexisting medical conditions or certain concomitant medications should have a cardiac evaluation and, if treated with GILENYA, should be observed overnight in a medical facility with continuous ECG monitoring.
- Patients with prolonged QTc interval at baseline or during the observation period, or at additional risk for QT prolongation or taking drugs with known risk of torsades de pointes should be observed overnight in a medical facility with continuous ECG monitoring.
- Patients receiving concurrent therapies that slow heart rate or AV conduction should be evaluated with possibility of switching off these drugs prior to initiation of GILENYA. In patients who cannot switch, overnight observation in a medical facility with continuous ECG monitoring is recommended.
- Reinitiation of therapy following discontinuation and appropriate monitoring:
  If GILENYA therapy is discontinued for more than 14 days after the first month of treatment, the effects on heart rate and AV conduction may recur on reintroduction of GILENYA treatment and

the same precautions (first dose monitoring) as for initial dosing should apply. Within the first 2 weeks of treatment, first dose procedures are recommended after interruption of one day or more; during week 3 and 4 of treatment, first dose procedures are recommended after treatment interruption of more than 7 days.

Contraindications

- recent (within last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure.
- history or presence of Mobitz Type II 2nd or 3rd degree AV block or sick sinus syndrome, unless patient has a functional pacemaker
- baseline QTc interval ≥ 500 msec
- treatment with Class Ia or Class III anti-arrhythmic drugs

Infections

GILENYA causes a dose–dependent, reversible sequestration of lymphocytes in lymphoid tissues resulting in a reduction of peripheral blood lymphocyte count to 20-30% of baseline values.

- Before initiating treatment with GILENYA, a recent CBC (i.e. within 6 months) should be available.
- Consider suspending treatment with GILENYA if a patient develops a serious infection, and reassess the benefits and risks prior to re-initiation of therapy.
- Patients without a history of chicken pox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody negative patients should be considered prior to commencing treatment with GILENYA, following which initiation of treatment with GILENYA should be postponed for one month to allow for full effect of vaccination to occur.
- The use of live attenuated vaccines should be avoided during and for 2 months after treatment with GILENYA because of the risk of infection.

Macular Edema

In clinical trials, macular edema occurred in 0.4% of patients who received GILENYA 0.5mg, predominantly within the first 3-4 months. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmologic examination. Macular edema generally improved or resolved with or without treatment after drug discontinuation, but some patients had residual visual acuity loss even after resolution of macular edema.

- An adequate ophthalmologic evaluation should be performed at baseline and 3-4 months after treatment initiation.
- If patients report visual disturbances at any time while taking GILENYA, additional ophthalmologic evaluation should be undertaken.
- Patients who have a history of uveitis or diabetes are at increased risk of macular edema. It is recommended that MS patients with diabetes mellitus or a history of uveitis undergo an ophthalmologic examination prior to initiating GILENYA therapy and have regular follow-up ophthalmologic evaluations while receiving GILENYA therapy.

Respiratory Effects

Small dose-dependent reductions in forced expiratory volume over one second (FEV1) and Diffusion Capacity of the Lung for Carbon Monoxide (DLCO) were observed in patients treated with GILENYA, as early as 1 month after treatment initiation. The changes in FEV1 appear to be reversible after treatment

discontinuation. There is insufficient information to determine the reversibility of the decrease of DLCO after drug discontinuation.

- Spirometric evaluation of respiratory function and evaluation of diffusion lung capacity for carbon monoxide (DLCO) should be performed during therapy with GILENYA if clinically indicated.

Hepatic Effects

Elevations of liver function tests may occur in patients receiving GILENYA. The majority of elevations occurred within 6-9 months.

- Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of GILENYA therapy.
- Liver enzymes should be monitored in patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. GILENYA should be discontinued if significant liver injury is confirmed. Patients with pre-existing liver disease may be at increased risk of developing elevated liver function tests when taking GILENYA.

Fetal Risk

Based on animal studies, GILENYA may cause fetal harm.

- There are no adequate and well-controlled studies of GILENYA in pregnant women.
- Women of childbearing potential should be counseled on the potential risk to the fetus and advised to use effective contraception during and for at least 2 months following discontinuation of GILENYA therapy.
- Women who become pregnant while on therapy must be counseled on potential risk to the fetus.
- GILENYA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy Registry

Since there are no adequate and well-controlled studies of GILENYA in pregnant women, a pregnancy registry has been established to collect information about the effects of GILENYA during pregnancy. Physicians are encouraged to register patients who become pregnant while exposed to GILENYA or within 2 months after stopping therapy.

Prescribers with an eligible patient, or patients themselves, can contact the Pregnancy Exposure Registry by calling Outcome at 1-877-598-7237, sending an email to gpr@outcome.com or visiting www.gilenyapregnancyregistry.com.

Patient Counseling

Prescribers should inform patients about the benefits and risks of GILENYA before a decision is made to prescribe. Patients should be instructed to read the Medication Guide. Patients should be given an opportunity to discuss the contents of the Medication Guide with their physician or healthcare professional and to obtain answers to any questions they may have.

Patients should especially be counseled on the safety information in the Medication Guide Section “What is the most important information I should know about GILENYA?”

Please see the accompanying full **Prescribing Information (updated May 2012)** for more information.

Reporting Adverse Events

Healthcare providers should report all suspected adverse events associated with the use of GILENYA. Please contact Novartis Drug Safety and Epidemiology at 1-888-NOW-NOVA (669-6682) or FDA at

1-800-FDA-1088 or www.fda.gov/medwatch.

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/s/

ERIC P BASTINGS
05/28/2013